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Bipolar Androgen Therapy: Can We Go Beyond Mere Androgenic Suppression for Prostate Cancer? A Mini-Review

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ABSTRACT

The Bipolar Androgen Therapy (BAT) is a novel strategy of treatment for metastatic Prostate Cancer (mPC), currently under investigation in many trials. The treatment schedule consists in alternating standard Androgen Deprivation Therapy (ADT) with testosterone injections in order to reach transitory supra-physiologic testosterone levels [1]. BAT aims to go beyond the continuous androgen suppression, which is up-to-date essential standard treatment for mPC in every phase of the disease, thus preventing adaptation of mPC cells to a persistent low-androgen environment [2].

New generation hormone therapies, such as enzalutamide and abiraterone, improved overall survival in mPC patients who progressed to ADT [3-6] and more recent trials suggest an even greater improvement of the outcomes when used in the hormone-sensitive phase [7-10]. However, resistance eventually occurs as mPC cells growth becomes partially independent of the androgen receptor (AR) [11]. Therefore, new strategies capable of delaying progression to metastatic castration resistant prostate cancer (mCRPC) and at the same tFime restoring sensitivity to hormone treatments are needed. In this context, BAT is attracting more and more interest amng researches.

Keywords: Bipolar, Androgen, Therapy, Prostate, Cancer, Review

INTRODUCTION

Supraphysiological stimulation of androgen receptor and its effect on mPC cells

AR plays a crucial role in mPC growth and progression in every phase of the disease [1-11]. Thus, the blockage of AR activity has represented the cornerstone of mPC treatment since the seminal work of Huggins and colleagues [12]. However, it has been proved that both AR pathway suppression and Supraphysiological Stimulation of AR (SSA) result in growth inhibition, significant decrease in cells in S and G2/M phases and apoptosis [13]. The mechanisms behind this phenomenon have not been fully understood yet.

AR is directly involved in cell cycle progression in mPC cells, acting as a licensing factor for the initiation of DNA replication between G1 and S phases [14,15]. As a major component of the pre-replication complex, AR needs to be degraded in early G1 phase in order to allow a new pre-replication complex to identify DNA binding sites. SSA leads to overstabilization of the replication complex bound to the DNA, thus preventing DNA re-licencing [16]. SSA may also induce mPC cells senescence and apoptosis through various interaction between AR pathway, cyclin dependent kinase inhibitor and apoptosis regulator BAX protein [17–19]. Moreover, SSA could results in direct DNA damage. Haffner et al. proved that SSA causes dsDNA

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breaks, increasing the activity of topoisomerase II beta [20]. These evidences suggest that the combination of SSA with DNA-directed chemotherapy, such as etoposide, could improve anti-tumour activity of SSA. Finally, a transitory restoration of AR activity may inhibit the expression of AR splice variants and the activation of alternative (AR-independent) growth pathways [21-23].

Experiences with BAT in clinical trials

Testosterone-based treatments in mPC have been largely investigated over the last 40 years [24]. However, only the most recent trials should be considered for the purpose of evaluating the efficacy of BAT, as only modern formulations of testosterone therapy are able to effectively achieve SSA [25]. Importantly, suspension of ADT alone is not enough to produce an acute raise in androgen levels, allowing mPC cells to promptly adapt to the new environment.

Schweizer et al. [26] enrolled 16 men with mCRPC to receive monthly testosterone intramuscular injections (at the dose of 400 mg), associated with etoposide 100 mg/day on day 1 to 14. Radiographic response rate was 50% (8/16). Most notably, 100% of men achieved PSA decline with subsequent second-line therapies, including 3 men that received a therapy they have already progressed to, suggesting that BAT may restore sensitivity to previous hormone-treatments [26]. In an open-label, phase 2 clinical trials, 30 patients with MCPc were treated with BAT after progression to enzalutamide. ORR was 50%. Among 29 patients who resumed enzalutamide after progression to BAT, PSA response rate and progression-free survival were 52% and 4.7 months, respectively [27]. In another trial, 33 treatment naïve patients with low metastatic burden prostate cancer or biochemically recurrent disease were treated with 3 months cycles of BAT plus continuous ADT, after six months of ADT alone. At the time point of 18 months, 59% of patients achieved PSA < 4 ng/mL, which was primary end point in this trial [28]. The treatment was safe and well-tolerated, with no severe adverse events detected. Lastly, 222 MCPc patients were enrolled in the TRASFORMER trial that randomized with a 1:1 ratio to testosterone cypionate/enanthate (400 mg of either agent injected intramuscularly every 28 days) or enzalutamide (160 mg/day). Results are available at clinicaltrials.gov. PFS was 5.62 months and 5.72 months, while radiographic progression was 5.75 months and 8.72 months for BAT and enzalutamide, respectively (NCT02286921).

FUTURE PERSPECTIVES AND CONCLUSIONS

BAT showed promising results in mPC patients, with a favourable safety profile and encouraging activity signals. However, phase III randomized clinical trial are needed to evaluate the real efficacy of BAT compared to standard therapies. At the moment, clinical trials are on-going to investigate the efficacy of BAT alone (NCT03522064), in association with olaparib (NCT03516812) and in association with nivolumab (NCT03554317) in mCRPC patients. Secondary outcomes, such as time to chemotherapy treatments and improvement in QoL, should be considered carefully when evaluating BAT. Moreover, as PSA may not be a reliable marker of response to BAT, future clinical trials should also consider different methods of response evaluation, which may also include, alongside CT and bone scans, liquid biopsy and direct evaluation of intracrine androgen biosynthesis achieved through direct tumour tissue assessment.

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